(a) plant cells containing nucleotide sequences encoding a biologically functional multimeric protein comprising at least two different polypeptides not normally produced by plants, wherein each nucleotide sequence encoding a polypeptide of the multimeric protein encodes a leader sequence forming a secretion signal that is cleaved from said polypeptide following proteolytic processing.

REMARKS

Claims 21, 24-40, 43, 50, 54-63 and 69-100 are currently pending following entry of the instant Amendment. The newly added claims are directed to various multimeric proteins and to the various forms of immunoglobulin obtained by processing the transgenic plant cells. The amended claims and the newly added claims are fully supported by the specification, and do not introduce new matter.

Applicants have deleted the phrase"one or more" in claim 21 to simplify reading of the claim. It should be understood that even though the claim recites "a biologically multimeric protein," the claim nonetheless reads on cells expressing more than one biologically functional multimeric protein. Claim 21 also has been amended to require that the multimeric protein comprise at least two different polypeptides. This was done to make clear that cells expressing heteromultimeric proteins are encompassed by the claim. Finally, claim 21 has been amended to require that the multimeric protein not normally be produced by "plants." This was done to make clear that the claims encompass cells expressing multimeric proteins that do not originate in plants.

During the interview at the Patent Office on April 25, 2002, the examiners requested that Applicant provide any potentially relevant art to which they are aware that is relevant to expression of multimers in plants. A supplemental IDS with 1449 form with new art is attached herewith. The following art is briefly discussed.

1. Beachy et al. EMBO J. (1985) 4:3047-3053 "Accumulation and assembly of soybean β-conglycinin in seeds of transformed petunia plants." The β-conglycinin is a multimeric protein of about 200 Kd in size, produced by assembly of three polypeptides, an α' subunit (76 Kd), an α subunit (72 Kd) and a β subunit (53 Kd). Beachy et al. reports the

expression of the α' subunit of soybean β-conglycinin in seeds of a petunia plant. The α' subunit is only a single polypeptide of a multimeric protein which protein is normally expressed by plants. Thus, Beachy et al. does not teach or suggest expression in plants of a biologically active multimeric protein comprising at least two different polypeptides not normally produced by plants.

2. Jefferson et al. EMBO J (1987) 6(13):3901-7 " GUS Fusions: β-glucuronidase as a sensitive and versatile gene fusion marker in higher plants." GUS-is a bacterial protein which is enzymatically active as a tetramer of the same subunit. Therefore, GUS in its active form comprise at least two different polypeptides. Thus, Jefferson et al. does not teach or suggest expression in plants of a biologically active multimeric protein comprising at least two different polypeptides not normally produced by plants.

3. Harpster et al., Mol Gen Genet (1988) 212:182-190," Relative strengths of the 35S cauliflower mosaic virus, 1', 2', and nopaline synthetase promoters in transformed tobacco sugarbeet and oilseed rape callus tissue " This reference compares the relative strengths of various plant promoters for expressing a chimeric gene prepared from the chitinase gene (*ChiA*) gene of *Serratia marcescens* and the octopine synthetase gene of *A. tumefaciens*. The activity of the expressed polypeptides were not determined by Harpster et al. See p. 189. It is Applicants' understanding that the ChiA gene and the octopine synthetase gene encode a single polypeptide that forms a homomultimer in its active state. Thus, Harpster et al. does not teach or suggest expression in plants of a biologically active multimeric protein comprising at least two different polypeptides not normally produced by plants.

4. Kavanaugh et al., Mol Gen Genet (1988) 215(1):38-45 "Targeting a foreign protein to chloroplasts using fusions to the transit peptide of a chlorophyll a/b protein." This reference reports plant expression of chimeric genes comprising fusion of various amino terminal segments of the mature chlorophyll a/b binding (Cab) apoprotein with the *E. coli* β-glucuronidase, the later known to be active as a tetramer of a single polypeptide. Thus, Kavanaugh et al. does not teach or suggest expression in plants of a biologically

active multimeric protein comprising at least two different polypeptides not normally produced by plants.

5. Iturriaga et al., The Plant Cell, (1989) 1:381-390 "Endoplasmic reticulum targeting and glycosylation of hybrid proteins in transgenic plants." This reference describes plant expression of a fusion protein between potato storage protein, patatin, and *E. coli* β-glucuronidase (GUS), the latter known to be active as a tetramer of a single polypeptide. Thus, Iturriaga et al. does not teach or suggest expression in plants of a biologically active multimeric protein comprising at least two different polypeptides not normally produced by plants.

6. Hofte et al., Microbiol Rev 1(989) Jun; 53(2):242-255, "Insecticidal Crystal Proteins of *Bacillus thuringiensis.*" This reference describes expression of the *Bacillus thuringiensis* (Bt) protein in plants. Bt is normally expressed as non glycosylated protein of 230 Kd comprising two identical polypeptides of 130 Kd in size. Bt protein is an inactive protoxin in the dimeric form (230 Kd) but becomes active in vivo following proteolytic cleavage to 64 to 71 kDa polypeptides. Thus, Hofte et al. does not teach or suggest expression in plants of a biologically active multimeric protein comprising at least two different polypeptides not normally produced by plants.

7. U.S. Patent no. 4,956,282 (Goodman et al.): This reference already of record describes expression of a fragment of mouse gamma interferon in plant cells. It is Applicants' understanding that gamma interferon forms a homomultimer in its biologically active form. Thus, Goodman et al. does not teach or suggest expression in plants of a biologically active multimeric protein comprising at least two different polypeptides not normally produced by plants.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

Atty. Dkt. No.: EPI3007D (071344-0304)
(formerly TSRI 184.2CON-3)

The Examiner is urged to contact the undersigned by telephone to address any outstanding issues standing in the way of an allowance.

Respectfully submitted,

Date: June 28, 2002

By _____

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

21. (Amended three times) A plant cell comprising:

(a) plant cells containing nucleotide sequences encoding [~~one or more~~] a biologically functional multimeric protein **comprising at least two different polypeptides** not normally produced by [~~the plant cell~~] **plants**, wherein each nucleotide sequence encoding a polypeptide of the multimeric protein encodes a leader sequence forming a secretion signal that is cleaved from said polypeptide following proteolytic processing.